UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/830,190	04/21/2004	Ananth Annapragada	27428-4	7714

21130 7590 09/04/2008

BENESCH, FRIEDLANDER, COPLAN & ARONOFF LLP
ATTN: IP DEPARTMENT DOCKET CLERK
2300 BP TOWER
200 PUBLIC SQUARE
CLEVELAND, OH 44114

EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	**PAPER NUMBER**
1618	

MAIL DATE	DELIVERY MODE
09/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/830,190
Filing Date: April 21, 2004
Appellant(s): ANNAPRAGADA ET AL.

Benjamin E. Kern (Reg. No. 56,391)
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/15/08 appealing from the Office action mailed 11/21/07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 1-4,6-11 and 25-33. The examiner inadvertently excluded the claim 26 in the heading of the obvious rejection but as evidenced by the PTO-326 form claim 26 is rejected. The rejection of the instant claim 26 was addressed in the body of the office action as the reference of Payne et al. was used and directly pointed out that the lipids utilized include those found in column 5, lines 64-65 which clearly states DPPC (see office action mailed 11/21/07, page 4, paragraph 10, line 2) and therefore the omission of the instant claim 26 in the heading of the obvious rejection was a typographical error.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: The examiner inadvertently excluded the claim 26 in the heading of the obvious rejection but as evidenced by the PTO-326 form claim 26 is rejected. The rejection of the instant claim 26 was addressed in the body of the office action as the reference of Payne et al. was used and directly pointed out that the lipids utilized include those found in column 5, lines 64-65 which clearly states DPPC (see office action mailed 11/21/07, page 4, paragraph 10, line 2) and therefore the omission of the instant claim 26 in the heading of the obvious rejection was a typographical error.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

November 21, 2007 Non-Final Office Action

Specification

Torchilin et al. (Biochim. Biophys. Acta 1996, 1279, 75-83)

US. Patent No. 4,744,989 issued to Payne et al.

Sachse et al. (Invest. Radiol 1997, 32, 44-50)

Leike et al. (Invest Radiol. 2001, 36, 303-308)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-4,6-11,25 and 27-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) in view of Payne et al. (US 4,744,989) and further in view of Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50; pages provided are numbered 1-8) or Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308).

Torchilin et al. (*Biochim. Biophys. Acta* **1996**, *1279,* 75-83) discloses a PEG and/or antibody substituted liposome which are long-circulating and target-specific (p76, paragraphs 2 and 3). The blood circulation time of the liposomes are improved by coating the surface with PEG by decreasing their opsonization and recognition by the liver (p76, paragraph 2). The targeting of liposomes to infracted myocardium is possible since normal myocardial cells do not permit extracellular macromolecules, such as antimyosin antibody, to traverse the cell membrane but necrotic cardiomyocytes with disrupted membranes cannot prevent the antibody from interacting with myosin (p76, paragraph 1). The liposomes are prepared by mixing PC, cholesterol and a PEG-PE (p77, paragraph 3). The liposomes of the disclosure include small liposomes of size 120-150 nm. According to appellants declaration filed 9/18/07, the recitation of "incorporated" (liposomes are radioactively labeled with the radioactive element via liposome-incorporated chelating agent DTPA (p77, paragraph 4) is defined as the external attachment of the radiolabeled contrast agent outside of the liposome. Therefore, prior to incorporation of the radioactively labeled contrast agent the targeted,

pegylated liposomes of the disclosure include small liposomes of size 120-150 nm (p77, preparation of liposomes). Torchilin et al. does not disclose the encapsulation of an iodinated contrast agents.

Payne et al. (US 4,744,989) discloses liposomes prepared from a combination of lipids (column 5, lines 64-65) and adjuvants, such as cholesterol where the mean size of the liposome can be controlled to suit the particular medicament, such as an iodinated contrast agent (column 6, lines 11-30) to be carried by the liposome (column 3, lines 31-33; column 4, lines 33-36; column 4, lines 59-62). The liposomes of the disclosure have a mean size from about 100 nm to 6 microns (column 4, lines 57-58). The size may be affected by the amount of phospholipids, the pH and hydration medium (column 5, lines 1-9). The method of preparing the liposomes includes subsequent removal of the unencapsulated material (column 6, lines 60-61).

Sachse et al. (*Invest. Radiol.***1997**, *32*, 44-50; pages provided are numbered 1-8) teaches of Iopromide-containing liposomes for enhancing CT imaging. The liposomes contain soy phosphatidylcholine (SPC), cholesterol, soy phosphatidylglycerol (SPG) (6:3:1 molar ratio) and 5 mol% DPSE-PEG2000 which are administered intravenously into a rat tail vein at a dose of 250mg I/kg (p3, paragraph 4) and show prolonged blood circulation with CT density differences above 70 HU (abstract; p2, paragraph 1). The CT blood pool imaging in a rabbit with DSPE-PEG liposomes show approximately 71ΔHU after 45 min (p5, paragraph 4; fig 6A-6D). Sachse et al. also discloses that the PEGylated lipid derivatives in the liposome membrane provides for potent increase in

circulation times (p1, paragraph 2) as they avoid the mononuclear phagocytic system (MPS) and target to non-MPS organs.

Leike et al. (*Invest. Radiol.* **2001**, *36*, 303-308) discloses a computed tomography enhancing iodinated liposome composition containing soy phosphatidylcholine (SPC), cholesterol and soy phosphatidylglycerol (SPG) (p303, last paragraph). The contrast enhancing liposomal agents have a mean diameter of 201 nm are used for prolonged blood-pool opacification upon intravenous injection of 300mg I/kg (p305, paragraphs 3 and 8; p306, fig 2) which encompass the compositions for enhancing contrast of the instant claims. The contrast enhancing iodinated liposome compositions of the disclosure are observed immediately after administration up to 60 min with a mean peak enhancement of in the aorta of approximately 90ΔHU (p305, last paragraph; p306, first paragraph).

At the time of the invention it would have been obvious to one skilled in the art to prepare targeted-pegylated liposomes of the size 120nm-150 nm (Torchilin et al.) and utilize/try them for the encapsulation of the iodinated contrast agents of Payne et al. as the liposomes of Payne et al. may also be 100 nm in size. Torchilin et al. teaches that the blood circulation time for PEG-LL (large liposomes) is less than that for PEG-SL (small liposomes) (p81, paragraph 1). The disclosures are drawn to the same products (liposomes) and the encapsulation of the contrast agents of Payne et al. into the liposomes of Torchilin et al. will have predictable results, as there are multiple factors for controlling the size of the liposomes. The substitution of different lipids as taught by Sachse et al. or Leike et al. for the lipids of Torchilin et al. is advantageous as they are

well suited for CT blood-pool imaging with iodinated contrast agents (Leike et al. p303, paragraph 1). In the case of small liposomes, Torchilin et al. (p80, small liposomes) teaches that grafting of PEG to the liposome surface sharply increases the liposomal circulation time due to the interaction of the PEG with plasma proteins (p80, small liposomes). Furthermore, it is obvious to vary and/or optimize the amount of (compound) provided in the composition, according to the guidance provided by (reference), to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

(10) Response to Argument

Appellant asserts that Torchilin et al. does not teach or suggest a liposome having a nonradioactive contrast enhancing agent encapsulated therein.

The reference of Torchilin et al. was not used to teach or suggest a liposome having a nonradioactive contrast enhancing agent encapsulated therein but was used to teach that prior to incorporation of the radioactively labeled contrast agent the targeted, pegylated liposomes of the disclosure include small liposomes of size 120-150 nm (p77, preparation of liposomes). The reference of Torchilin et al. was used to teach of the preparation of these small liposomes where they contain a lipid, a pegylated lipid and cholesterol which encompass the lipid, pegylated lipid and cholesterol of the instant claims 1 and 25.

Appellant asserts that Torchilin et al. is not directed to enhancing contrast of one or more areas of a subject for X-ray imaging.

The reference of Torchilin et al. was not used to teach of enhancing contrast of one or more areas of a subject for X-ray imaging. Also, the intended use of, "enhancing contrast of one or more areas of a subject for X-ray imaging" is not afforded any patentable weight. "The recitation of a new intended use for an old product does not make a claim to that old product patentable." *In re Schreiber*, 44 USPQ2d 1429 (Fed. Cir. 1997).

Appellant asserts that Payne et al. purports to achieve the preparation of a "final liposome product of desired size, such as a mean diameter of within the range of from about 25 nm to about 12 μm". However, Payne et al. teaches that the composition of the liposomes used is a key determinant of their size. Important in relation to this principle is the fact that Payne et al. does not teach or even suggest a liposome having lipids or phospholipids which are derivatized with a polymer.

The reference of Payne et al. was not used to teach of a liposome having lipids or phospholipids which are derivatized with a polymer but used to teach that liposomes of sizes 100 nm to 6 μm, which includes the less than 120 or less than 150 nm liposomes of the instant claims, may encapsulate a nonradioactive iodinated contrast agent. The reference of Torchilin et al. was used to teach that prior to incorporation of the radioactively labeled contrast agent the targeted, pegylated liposomes of the disclosure include small liposomes of size 120-150 nm (p77, preparation of liposomes). The reference of Torchilin et al. was used to teach of the preparation of these small

liposomes where they contain a lipid, a pegylated lipid and cholesterol which encompass the lipid, pegylated lipid and cholesterol of the instant claims 1 and 25.

Appellant asserts that Sachse et al. does not teach liposomes having polymer-chain derivatized phospholipids wherein the liposomes have an average diameter of less than 150 nm but teaches liposomes having a mean diameter of 204 nm. Rather, Sachse specifically teaches that the inclusion of DSPE-PEG leads to a "drastic increase in vesicle size."

Sachse et al. was not used to teach liposomes having polymer-chain derivatized phospholipids wherein the liposomes have an average diameter of less than 150 nm but was used to teach of liposomes containing soy phosphatidylcholine (SPC), cholesterol, soy phosphatidylglycerol (SPG) (6:3:1 molar ratio) and 5 mol% DPSE-PEG2000 which show prolonged blood circulation with CT density differences above 70 HU. Payne et al. teaches that the sizes of final liposomes can be controlled to suit the particular medicament to be carried by the liposome where a negatively-charged phospholipids, such as DPPC is used to decrease the size of the final liposomes. It is disclosed by Torchilin et al. that pegylated lipids may be used to generate small liposomes of sizes 120 nm and 150 nm. Therefore it would have been obvious to one skilled in the art to use a pegylated lipid in combination with a negatively-charged phospholipid, such as DPPC to generate a small size liposomes, such as 120 nm and 150 nm.

Appellant asserts that Leike et al. does not teach phospholipids derivatized with polymer chains and does not teach liposomes having polymer-chain derivatized

phospholipids wherein the liposomes have an average diameter of less than 150 nm but teaches liposomes having a mean diameter of 201 nm.

Leike et al. was not used to teach phospholipids derivatized with polymer chains and does not teach liposomes having polymer-chain derivatized phospholipids wherein the liposomes have an average diameter of less than 150 nm. The reference of Leike et al. was used to teach of a computed tomography enhancing iodinated liposome composition containing soy phosphatidylcholine (SPC), cholesterol and soy phosphatidylglycerol (SPG).

Appellant asserts that the office's rejection of claim 26 without providing a basis is improper and should be reversed.

The examiner inadvertently excluded the claim 26 in the heading of the obvious rejection but as evidenced by the PTO-326 form claim 26 is rejected. The rejection of the instant claim 26 was addressed in the body of the office action as the reference of Payne et al. was used and directly pointed out that the lipids utilized include those found in column 5, lines 64-65 which clearly states DPPC (see office action mailed 11/21/07, page 4, paragraph 10, line 2) and therefore the omission of the instant claim 26 in the heading of the obvious rejection was a typographical error. The two lines of Payne et al. column 5, lines 64-65 referred to clearly states DPPC (see office action mailed 11/21/07, page 4, paragraph 10, line 2) directly point to the use of DPPC.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Melissa Perreira/

Examiner, Art Unit 1618

Conferees:

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617